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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,430	03/09/2005	Jeffery A Bibbs	DIAKR.007NP	5428

20995 7590 01/21/2009

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EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
01/21/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/527,430	BIBBS, JEFFERY A	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *7-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets, 5 December 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I in the reply filed on 21 October 2008 is acknowledged.

Claims 7-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group II and III, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 21 October 2008.

Election/ Restriction

In response to the Restriction Requirement, Applicants hereby elect Group I (Claims 1-6). Applicants reserve the right to pursue the remaining claims in a divisional application(s). Claims 1-6 read upon the elected invention. The Examiner has also required an election of one specific and exact T-channel compound (either Formula I or II). In response to this Election of Species Requirement, Applicants hereby elect formula I. Within formula I, Applicants elect the following substituents for the R groups: RI=CH3, R2=CH3, R3=CH3, R4=CH3, R5-CH (CH3)2, R6=H, R7=H, R8=H, R9=C15H31, R10=H. Since formula II was not elected, election of substituents for R11-R20 does not apply. Since Group III (claims 9-11) was not elected, election of whether the testing step will be done *in vitro* or *in vivo* according to claims 10 and 11 does not apply.

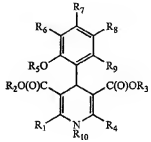
Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification

(I) 

while being enabling for formula I, wherein, Applicants elect the following substituents for the R groups: RI=CH3, R2=CH3, R3=CH3, R4=CH3, R5-CH (CH3)2, R6=H, R7=H, R8=H, R9=C15H31, R10=H, does not reasonably provide enablement for any and all such T-type calcium channel blockers that exhibit the same activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Exparte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in ***In re Wands***, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims

The nature of the invention is drawn to the art of treating hypertension and hypertensive disorders.

The quantity of experimentation necessary in order to determine the scope of the instant claim 1 lacks enablement because the limitation drawn to a selective T-channel antagonist is broad and would reasonably include a plethora of agents in the said class of antihypertensive agents. This variable list of Markush members would result in undue experimentation because having to determine the activity of each and every T-type antagonist would be burdensome. The amount of direction and guidance in order to clearly determine each and every T-type channel antagonist would meet each and every limitation of claim 1 is absent in the specification.

Bui et al. (The Mibefradil Derivative NNC55-0396, a Specific T-Type Calcium Channel Antagonist, Exhibits Less CYP3A4 Inhibition than Mibefradil, DMD 36: 1291-1299, 2008, printed pages 1-40, reflects the state of the art by teaching a derivative of Mibefradil (NNC55-0396) which is more selective than it's parent compound, Mibefradil (please see the whole abstract , especially the last sentence).

Bui et al. also teach a critical safety issue as to whether Mibefradil (NNC55-0396) has a more favorable P450 inhibition profile than Mibefradil because such information would predict its potential for drug interactions. Based on the experimentation, it was conjectured that the (NNC55-0396), may have, despite structural similarities, a more benign P450 inhibition profile than Mibefradil (p. 4 of 20, 2nd full paragraph).

Thus, unpredictability would be high with regard to determining that any and all T-Type channel blockers would exhibit the same therapeutic efficacy in view of the variable disease states treated as disclosed. Bui et al. discloses the P450 inhibition profile which is well-known in the art of biopharmaceutics in order to reasonably correlate and determine which agents may present more bioavailability.

The breadth of the claims is not commensurate in view of the scope of the claimed invention. Claim 1 teaches a broad limitation that is not reasonably supported by the specification. Whereas, claim 1 suggests that T-Type channeling antagonists collectively as a class can treat the myriad of disorders related to hypertension. However, the instant specification is silent of any disclosure which clearly delineates and teaches that any and all selective T-channel antagonist may reduce systolic blood pressure *in vivo* of at least 3 hours and a duration of activity *in vivo* for at least 24 hours.

It is further emphasized that it would require undue experimentation for one of ordinary skill to find a T-channel antagonist having the activity defined in claim 1. The activity disclosed within the instant claim contains limitations that is absent of explanation in the specification with regard this shared activity by any and all T-type antagonists.
Another consideration is whether the invention produces a "concrete" result. Usually, this

question arises when a result cannot be assured. In other words, the process must have a result that can be substantially repeatable or the process must substantially produce the same result again. In re Swartz, 232 F.3d 862, 864, 56 USPQ2d 1703, 1704 (Fed. Cir. 2000) (where asserted result produced by the claimed invention is "irreproducible" claim should be rejected under section 101). The opposite of "concrete" is unrepeatable or unpredictable. Resolving this question is dependent on the level of skill in the art. For example, if the claimed invention is for a process which requires a particular skill, to determine whether that process is substantially repeatable will necessarily require a determination of the level of skill of the ordinary artisan in that field. An appropriate rejection under 35 U.S.C. 101 should be accompanied by a lack of enablement rejection under 35 U.S.C. 112, paragraph 1, where the invention cannot operate as intended without **undue experimentation**. See infra.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, and 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kumar et al. Kumar et al. teach the elected species as described above (please see page 651, structure of first column, represented by PPK 1-16, specifically see Table 1, PPK-5, which teach each and

every constituent as elected for formula 1, wherein R is CH (CH3)2, R1 is CH3, R2 is CH3, R9 of the current invention is identically duplicated on structure PPK 1-16.

Kumar et al. teach the use of PPK-5 (the moiety that teaches on the elected compound specifically) in the blocking of T-Type Calcium Channels (see page 654, column 1, 1st full paragraph).

Thus, Kumar et al. teach the current invention in view of the limitations disclosed. The inherent activities of T-Type Calcium Channel Antagonists are also adequately supported and suggested by Kumar et al. based on Figure 6, parts A and B, which teach and elucidate the anticipated activity of PPK-5 in comparison to Nifedipine, a well-known T-Type Calcium Channel Antagonist.

With regard to the limitation "in regular doses no more often than once per day", the MPEP cites thus:

I. SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). **Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.** In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In In re Crish, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), […].**The court stated that "just as the discovery of properties of a known material does not make it novel,**

the identification and characterization of a prior art material also does not make it novel." Id.< See also MPEP § 2112.01 with regard to inherency and product-by-process claims and MPEP § 2141.02 with regard to inherency and rejections under 35 U.S.C. 103.

Thus, the limitation "in regular doses no more often than once per day" is an inherent use of any pharmaceutical composition administered by mouth to a patient in need of such treatment. It would be instantly apparent to the one of skill in the pertinent art that a T-channel agonist oral composition would be given *at least* once per day which reasonably encompasses in anticipation the limitation of the current invention which discloses "in regular doses no more often than once per day".

Further, absent of any indication in the specification with regard to what is meant by the term "regular", the said term is given its broadest interpretation in view of the scope of the claimed invention. In this said case, a regular dose would be characterized as a concentration sufficient to affect a physiological change in a mammal body. Kumar et al. as a result fully anticipates the claimed invention by teaching a concentration ranging from 0.3 μM-3 μM of PPK-5 on transiently expressed on T-type channels obtained from 11 different cells (please see Figure 6, graphs A and B).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumar et al. (Synthesis and Evaluation of a New Class of Nifedipine Analogs with T-Type Calcium Channel Blocking Activity, Mol. Pharmacol. 61: 649-658, 2002 in view of Kobrin et al. (Safety of Mibefradil, a New Once-A-Day, Selective T-Type Calcium Channel Antagonist, The American Journal of Cardiology, Vol. 80 [48], 1997, printed pages 1-7) in view of Li et al. (USPGPUB 2001/0049447 A1).

For the reasons already disclosed above, Kumar et al. is reapplied in obviousness over claimed invention.

Additionally, Kumar et al. teach the similarities with regard to mechanisms of action with the compound as elected and the drug, Nifedipine (page 654, col. 2, page 655, 1st col., 1st paragraph).

Kumar et al. does not teach "prodrug".

However, Li et al. resolves the deficiency of Kumar et al. in view of the limitations contained in the current invention by teaching [...] prodrugs, the compounds of the present invention may additionally or alternatively be prepared to be delivered in a prodrug form. The term prodrug indicates a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions [0021].

Li et al. teach embodiments replete with T-type channel antagonist such as nifedipine which was indicated in Kumar et al. as having similar P450 inhibition profile and mechanisms of action as the elected compound.

Li et al. does not teach once a day dosing of a T-Type channel antagonist.

However, Kobrin et al. resolves the deficiency in Li et al. by teaching the once a day dosing of Mibefradil, a conventional T- Type channel antagonists. Further, Kobrin et al. disclose methods which include nifedipine which was indicated in Kumar et al. as having the same affinity toward the same receptors as the chemical moiety as elected (PPK-5 in the Kumar reference) (please see Methods, 2nd column, 1st full paragraph).

Thus, it would have been prima facie obvious to the one of skill at the time of invention to recognize a reasonable expectation of success via the combining the incorporating together the teachings and methods of Kumar et al., Li et al. and Kobrin et al.

In determining the scope and content of the prior art, Kumar et al. adequately teach subject matter which is obvious over the claimed invention. Kumar et al. teach the elected moiety disclosed as PPK-5, which is similar in activity to nifedipine (a well-known selective inhibitor). Li et al. teach T-Type channel antagonists as prodrugs which makes claim 4 obvious. Kobrin et al. teach a pharmaceutical composition comprising an art-known T-type inhibitors such as Mibefradil and nifedipine which are indicated in a regimen for once-a-day administration.

In view of the teachings of Kumar et al., the said reference clearly teaches the similarities of nifedipine with regard to the elected species. The elected compound is taught expressly throughout the Kumar et al. reference. However, agents such as nifedipine are further elucidated with reference to clear therapeutic regimens. This is the ascertained difference between the prior art and the claims at issue.

In considering objective evidence present in the application indicating obviousness, the one of skill would readily be inclined to recognize that if nifedipine and Mibefradil exemplify the same mechanisms of action as the elected compound and/ or vice-versa, then the claimed invention is thus overcome by obviousness in the teachings and methods of the references disclosed *supra.*

With regard to the limitation "in regular doses no more often than once per day", the MPEP cites thus:

I. SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE

UPON THE DIS-COVERY OF A NEW PROPERTY

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). **Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.** In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In In re Crish, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), […].**The court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel."** Id.< See also MPEP § 2112.01 with regard to inherency and product-by-process claims and MPEP § 2141.02 with regard to inherency and rejections under 35 U.S.C. 103.

Thus, the limitation "in regular doses no more often than once per day" is an inherent use of any pharmaceutical composition administered by mouth to a patient in need of such treatment. It would be instantly apparent to the one of skill in the pertinent art that a T-channel agonist oral composition would be given *at least* once per day which reasonably encompasses in obviousness over the limitation of the current invention which discloses "in regular doses no more often than once per day".

Further, absent of any indication in the specification with regard to what is meant by the term "regular", the said term is given its broadest interpretation in view of the scope of the

claimed invention. In this said case, a regular dose would be characterized as a concentration sufficient to affect a physiological change in a mammal body. Kumar et al. as a result fully anticipates the claimed invention by teaching a concentration ranging from 0.3 μM-3 μM of PPK-5 on transiently expressed on T-type channels obtained from 11 different cells (please see Figure 6, graphs A and B).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617

TEB